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THE SPECIFIC NATURE OF ANAPHYLAXIS.*

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FROM our first studies upon hypersusceptibility we were interested in the question "Is this reaction specific?"

In our work upon the toxic action of horse serum[1] we showed that this reaction is quantitatively specific for serums. That is, guinea-pigs sensitized with horse serum are subsequently very susceptible to a second injection of horse serum, but only slightly if at all susceptible to a second injection of the serum of other animals, such as rabbit, cat, dog, hog, sheep, chicken, or man. Conversely, guinea-pigs sensitized with the serum of these other animals are not very sensitive to a second injection of horse serum, whereas, they respond actively to a subsequent injection of the same serum used for the first injection.

We have further shown[2] that the specific nature of this phenomenon is more marked when proteid substances of widely different nature are used at the first and second injections. Thus a guinea-pig sensitized with horse serum does not react to a subsequent injection of egg-white, vegetable proteid, or milk. A guinea-pig sensitized with egg-white does not react to a subsequent injection of horse serum, vegetable proteid, or milk. A guinea-pig sensitized with milk does not react to the other proteid substances mentioned.

We have recently succeeded in demonstrating more clearly the specific character of the phenomenon we are studying by proving that guinea-pigs may be in a condition of anaphylaxis to three proteid substances at the same time. For instance, a guinea-pig may be sensitized with egg-white, milk, and horse serum and subsequently react to a second injection of each one of these substances. The guinea-pig may be sensitized by giving these strange proteids either at the same time or at different times, in the same place or in dif-

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[1] *Hyg. Lab., Bull. 29*, U. S. Pub. Health & Mar.-Hosp. Serv. Washington, April, 1906, pp. 1–95.

[2] *Hyg. Lab., Bull. 36*, U. S. Pub. Health & Mar.-Hosp. Serv. Washington, April, 1907, pp. 1–67.

ferent places, or by injecting them separately or mixed. The guinea-pig differentiates each anaphylactic-producing proteid in a perfectly distinct and separate manner. The animal is susceptible to the second injection of each one of the three substances in the same sense that it is susceptible to three separate infectious diseases.

These experiments, which we now wish to record, were divided into three series. In the first, the guinea-pigs were sensitized with horse serum, egg-white, and milk, in different parts of the body but at the same time. In the second series the three substances were thoroughly mixed and then injected into the guinea-pig. In the third series the animal was first given an injection subcutaneously of milk, 14 days later an injection of egg-white, and 14 days after that an injection of horse serum.

All of the animals, after at least 14 days from the last injection, were then given the second injection of one of these substances· Those animals that survived the injection of the first substance were

TABLE 1.

GUINEA-PIGS SENSITIZED AT THE SAME TIME, BUT IN DIFFERENT PLACES.

May 15, 1907, the following guinea-pigs received 1/250 c.c. of normal horse serum, 1 c.c. of a solution of egg-white in normal salt solution, and 1 c.c. of whole milk; the injections were given subcutaneously at about the same time but in different parts of the body. The animals were subsequently tested as follows:

Date	No. of G.-P.	Amount	Substance Injected	Method of Inoculation	Interval in Days since First Injection	Result
June 10, 1907	1,008	6 c.c.	Horse (roan) serum	Peritoneum	26	Very severe symptoms
‘ 11, 1907	1,008	6	Whole milk	Subcutaneous	27	Severe symptoms
" 12, 1907	1,008	6	Egg-white in salt solution	Peritoneum	28	Dead 25 minutes
" 11, 1907	1,009	6	Whole milk	Subcutaneous	27	Marked symptoms
" 12, 1907	1,009	6	Egg-white in salt solution	Subcutaneous	28	Severe symptoms
" 13, 1907	1,009	6	Horse (roan) serum	Peritoneum	29	Marked symptoms
" 11, 1907	1,010	6	Egg-white in salt solution	Subcutaneous	27	Severe symptoms
" 12, 1907	1,010	6	Whole milk	Subcutaneous	28	Severe symptoms
" 13, 1907	1,010	6	Horse (roan) serum	Peritoneum	29	Severe symptoms
" 11, 1907	1,011	6	Egg-white in salt solution	Subcutaneous	27	Dead 50 minutes
" 11, 1907	1,012	6	Whole milk	Subcutaneous	27	Marked symptoms
" 12, 1907	1,012	6	Egg-white in salt solution	Subcutaneous	28	Very severe symptoms
" 13, 1907	1,012	6	Horse (roan) serum	Peritoneum	29	No symptoms
July 1, 1907	1,012	6	Horse (roan) serum	Peritoneum	46	Very severe symptoms

given, usually after an interval of one day, one of the other substances used, and those withstanding it were finally tested for susceptibility to the third substance used. As will be seen from the detailed experiments, some of the animals survived after having had severe symptoms as a result of injections of all three of the proteids used. The detailed experiments and comments are given in Table 1.

From this table it will be seen that the pigs (Nos. 1,009, 1,010, 1,012) survived after having severe symptoms following the second injection of each of the three substances used. One (No. 1,011) died as a result of the injection of the egg-white, the first substance with which it was tested. One pig (No. 1,008) resisted the second injections of the horse serum and milk after severe reactions but died from the final injection of egg-white. It is therefore plain that guinea-pigs can be sensitized to horse serum, egg-white and milk at the same time, when the first injection is made in different parts of the body.

TABLE 2.

Guinea-Pigs Sensitized by Proteid Mixtures at Same Time and Place.

May 15, 1907, the following guinea-pigs received 1 c.c. whole milk, 1 c.c. saturated solution of egg-white in salt solution, and 1/250 c.c. of normal horse (roan) serum. These substances were well mixed before being injected subcutaneously into the guinea-pig. The pigs were subsequently tested as follows:

Date	No. of G.-P.	Amount	Substance Injected	Method of Inoculation	Interval in Days since First Injection	Result
June 10, 1907	1,013	6 c.c.	Horse (roan) serum	Peritoneum	26	Very severe symptoms
" 11, 1907	1,013	6	Whole milk	Subcutaneous	27	Marked symptoms
" 12, 1907	1,013	6	Egg-white in salt solution	Peritoneum	28	Dead 50 minutes
" 11, 1907	1,014	6	Whole milk	Subcutaneous	27	Marked symptoms
" 12, 1907	1,014	6	Egg-white in salt solution	Subcutaneous	28	Dead 120 minutes
" 11, 1907	1,015	6	Egg-white in salt solution	Subcutaneous	27	Dead 48 minutes
" 11, 1907	1,016	6	Whole milk	Subcutaneous	27	Marked symptoms
" 12, 1907	1,016	6	Egg-white in salt solution	Subcutaneous	28	Very severe symptoms
" 13, 1907	1,016	6	Horse (roan) serum	Peritoneum	29	No symptoms
July 1, 1907	1,016	6	Horse (roan) serum	Peritoneum	46	Marked symptoms
June 11, 1907	1,017	6	Egg-white in salt solution	Subcutaneous	27	Dead 45 minutes

From this series it will be seen that one guinea-pig (No. 1,016) reacted to, but survived the second injection of each of the substances used. One (No. 1,013) died as a result of the second injection of egg-white, this being the third of the substances for which the animal was tested, the other two having caused symptoms. One (No 1,014) died following the injection of egg-white, the second substance used. Two (Nos. 1,015 and 1,017) died following the injection of egg-white, the first substance tested. From this it

TABLE 3.

GUINEA-PIGS SENSITIZED AT DIFFERENT TIMES AND IN DIFFERENT PLACES.

May 13, 1907, the following guinea-pigs were given 1 c.c. whole milk; May 29, 1907, 1 c.c. saturated solution egg-white in salt solution; and on June 12, 1907, 1/250 c.c. normal horse (roan) serum. All injections were given subcutaneously. The pigs were subsequently tested as follows:

Date	No. of G.-P.	Amount	Substance Injected	Method of Inoculation	Interval in Days since First Injection of Corresponding Proteid	Result
June 29, 1907	1,021	3 c.c.	Egg-white in salt solution	Subcutaneous	30	Dead 18 minutes
" 29, 1907	1,026	2	Egg-white in salt solution	Subcutaneous	30	Dead 50 minutes
" 29, 1907	1,027	3	Egg-white in salt solution	Peritoneum	30	Dead 15 minutes
" 29, 1907	1,019	5	Horse (roan) serum	Peritoneum	17	Very severe symptoms
July 3, 1907	.....	6	Whole milk	Peritoneum	48	Severe symptoms
" 3, 1907	.....	6	Egg-white in salt solution	Subcutaneous	34	Dead 40 minutes
June 29, 1907	1,018	6	Whole milk	Peritoneum	44	Very severe symptoms
July 1, 1907	.....	6	Horse(roan) serum	Peritoneum	19	Mild symptoms
" 3, 1907	.....	3	Egg-white in salt solution	Peritoneum	34	Marked symptoms
June 29, 1907	1,022	6	Whole milk	Peritoneum	44	Severe symptoms
July 1, 1907	.....	5	Horse (roan) serum	Peritoneum	19	Mild symptoms
" 3, 1907	.....	3	Egg-white in salt solution	Peritoneum	34	Dead 30 minutes
June 29, 1907	1,024	5	Whole milk	Peritoneum	44	Very severe symptoms
" 29, 1907	.....	6	Horse (roan) serum	Peritoneum	17	No symptoms
July 1, 1907	.....	6	Horse (roan) serum	Peritoneum	19	No symptons
" 3, 1907	.....	3	Egg-white in salt solution	Peritoneum	34	Mild symptoms
June 29, 1907	1,020	3	Horse (roan) serum	Peritoneum	17	Very severe symptoms
" 29, 1907	.....	6	Whole milk	Peritoneum	44	No symptoms
July 1, 1907	.....	6	Horse (roan) serum	Peritoneum	19	No symptoms
" 3, 1907	.....	3	Egg-white in salt solution	Peritoneum	34	Severe symptoms
June 29, 1907	1,025	6	Horse (roan) serum	Peritoneum	17	Very severe symptoms
July 3, 1907	.....	6	Whole milk	Peritoneum	48	Severe symptoms
" 3, 1907	.....	.....	Egg-white in salt solution	Subcutaneous	34	Very severe symptoms

appears that guinea-pigs can be sensitized at the same time to horse serum, egg-white, and milk, when these three substances are mixed and then injected into the animal.

This table shows that four guinea-pigs (Nos. 1,018, 1,024, 1,020, 1,025) reacted to, but survived a second injection of all three of the substances used. Two guinea-pigs (Nos. 1, 019 and 1,022) died as a result of the second injection of egg-white, this being the third of the substances with which they were tested. Three (Nos. 1,021, 1,026, 1,027) died from a second injection of egg-white, the first substance with which they were tested.

Attention is drawn especially to guinea-pig No. 1,019. This animal reacted sharply to the second injection of milk. The guinea-pig presented the usual symptoms from which it gradually recovered. *Five hours* after the injection of milk, it was given an injection of egg-white from which it died. These two reactions in so brief a time seem to accentuate the specific nature of the phenomenon we are studying. It also adds weight to our belief that profound chemical changes probably in the central nervous system explain the essential features of the reaction, rather than morphologic alterations.

TABLE 4.

The two following guinea-pigs served as control for the above three series:

Date	No. of G.-P.	Amount	Substance Injected	Method of Inoculation	Previous Treatment	Interval in Days	Result
June 11, 1907	7,841	6 c.c.	Whole milk	Subcutaneous	Tox. 9.24 + 1/330 antitox. serum Alex. 192	111	No symptoms
" 29, 1907	....	6	Horse (roan) serum	Peritoneum	....	18	+ 45
" 29, 1907	7,848	6	Egg-white in salt solution	Subcutaneous	Tox. 9.24 + 1/300 antitox. serum Alex. 192	111	No symptoms
" 29. 1907	.....	6	Horse (roan) serum	Peritoneum	....	18	+ 12

This table shows that guinea-pigs are not sensitized by a previous injection of horse serum to a subsequent injection of milk or egg-white. When tested against horse serum they both died.

CONCLUSIONS.

Guinea-pigs may be sensitized to three strange proteids, viz., blood serum, egg-white, and milk, at the same time. The hypersusceptibility to each proteid substance is manifested by a second injection of the corresponding proteid. The three reactions are as distinct and specific as three separate infectious diseases. We, therefore, feel justified in concluding that the phenomenon of anaphylaxis is specific. We further believe that this work indicates that chemical changes, rather than morphological alterations, lie at the basis of this reaction.